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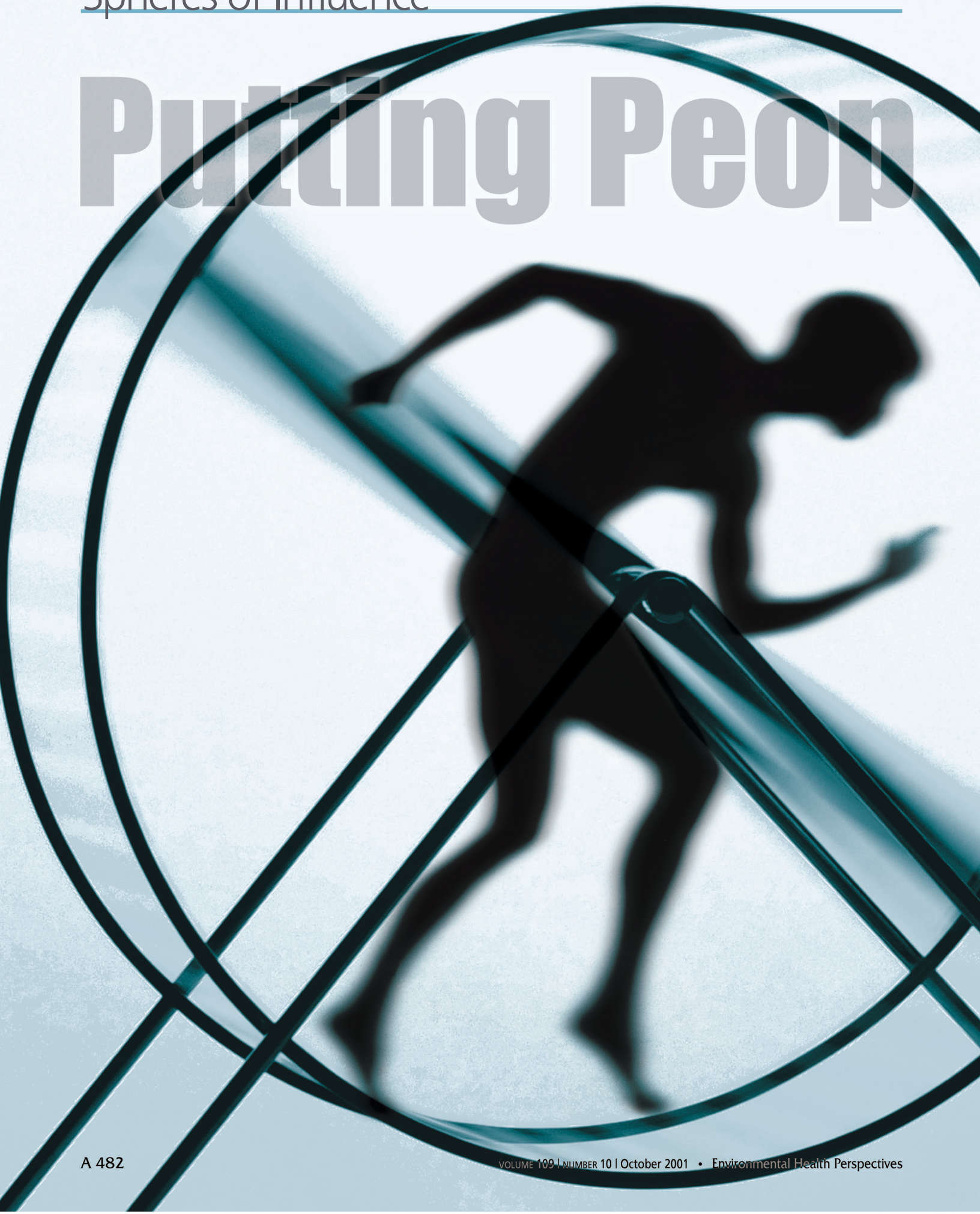

le to the Test

The thought of deliberately exposing people to pollutants sends a shudder down the spine of many people.

But when the complex reactions of humans to harmful substances can't be evaluated any other way, deliberate exposures can be justified for certain research, says Jane Koenig, a professor of environmental health at the University of Washington School of Public Health and Community Medicine. "There are no good animal models for asthma," she says. "We don't even know what asthma is in humans. [And] you can't tell a rat to take a deep breath. You can't ask them [about] symptoms, how they feel."

Reuther/EHP, Greenwell/EHP, DigitalVision

However, concerns about human studies are surfacing in the wake of news reports of deaths among human subjects. In 1999, an 18-year-old man died during a University of Pennsylvania gene transfer trial. In June 2001, a woman in a Johns Hopkins asthma study died after inhaling a test substance. And controversy erupted in March 2001 following reports in *The Seattle Times* about high death rates in a trial conducted from 1981 to 1993 at the Fred Hutchinson Cancer Research Center.

Government agencies and researchers in the United States and around the world have begun to respond to these and other emerging problems with a series of recommendations. For example, the U.S. Environmental Protection Agency (EPA) asked its Science Advisory Board in 1998 to review the use of human test data, particularly in regards to making pesticide registration decisions. But few recommendations have been implemented. Meanwhile, the parameters guiding the use of human subjects are "a morass," says Jeffrey Kahn, director of the Center for Bioethics at the University of Minnesota in Minneapolis and a member of the EPA Science Advisory Board.

An Aging System Unravels

In the aftermath of the post–World War II Nuremberg trials, which dealt in part with abuses of people during biomedical experiments, a broad set of standards for the use of human test subjects has evolved. In the United States, the latest generation of standards, known as the Common Rule, applies to 17 federal agencies, but not to organizations in the private sector that don't receive federal funding or that haven't committed to following the Common Rule.

These standards have helped protect people to some degree as they have participated in experiments designed to support public health standards for pollutant exposures. However, the broad language of the Common Rule has many grey areas, and questions about those areas are being raised in the course of the accelerating pace of health research and associated financial and professional conflicts and pressures. There also is a shortage of funding for oversight, and an inability to pin down what the costs of oversight even are. And organizations are generally unable to develop ethical parameters as rapidly as they create technological advances.

Despite the system's flaws, Richard Sharp, a biomedical ethicist at the NIEHS, agrees with Koenig that the use of human test subjects can be justified in certain circumstances. In most cases, studies of harmful substances are conducted on people already exposed at work, home, or play, or in an accident.

However, those studies and complementary laboratory and animal studies still leave knowledge gaps. To help plug those gaps, government and private researchers conduct an unknown number of studies involving deliberate exposures.

Most deliberate exposure studies sponsored by the EPA involve common air pollutants such as ozone or particulates, says Peter Preuss, director of the EPA's National Center for Environmental

Research. In other studies sponsored by the EPA and the NIH, people have been exposed for short periods of time to low doses of substances such as toluene, xylene, chlorobenzene, the gasoline additive MTBE, and the parasite *Cryptosporidium*. Recent overseas studies have exposed people to pesticides, says Richard Wiles, senior vice president of the Washington, D.C.–based advocacy organization Environmental Working Group (EWG). Private companies, such as chemical manufacturers, also conduct such research, sometimes under no obligation to adhere to government standards.

"The current system for protecting human subjects in large-scale multicenter trials is outdated," conclude Duke University's Michael Morse, Robert Califf, and Jeremy Sugarman in a report published in the 7 March 2001 issue of the *Journal of the American Medical Association*. "It charges IRBs [institutional review boards] with functions that they cannot credibly perform." The authors also criticize the adversarial yet symbiotic relationships between IRBs and data monitoring committees, which sometimes are used to independently assess a study and protect test subjects, thereby putting them in the position of both acting as watchdog and working to keep a study on track.

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People at Risk

Under the current regulatory framework, human test subjects are most vulnerable to harm after a study begins, says Greg Koski, director of the Office for Human Research Protections, formed within the U.S. Department of Health and Human Services (HHS) in 2001, partly in response to the death in the 1999 University of Pennsylvania gene transfer trial. For instance, participants often do not understand that they can back out of a study (for example, as they begin to feel side effects), and little is done to make sure that a volunteer isn't getting cold feet partway through a study, he says.

Other problems occur even before a study begins, when many volunteers likely sign the typical consent form without fully understanding the risks they will face. "[The informed consent process] is well-intended, but it falls short of the mark," Koski says. Some of the stumbling blocks with informed consent are subtle. "Like a lot of things, the devil is in the details," Sharp says. If the form cautions that a person might suffer from "peripheral neuropathy" as a result of a test, for instance, that may not mean as much to a layperson as the words "numbness in the hands or feet."

Janet Heinrich, director of health care and public health issues at the U.S. General Accounting Office, agrees. In May 2001 testimony published prior to presentation before the Subcommittee on Public Health of the Senate Committee on Health, Education, Labor, and Pensions, she said, "While the guidance and information on informed consent are extensive, [the National Bioethics Advisory Commission] has suggested that in general, the federal guidance continues to emphasize documenting the subject's consent rather than focusing on the ethical practices for obtaining this consent."

On a broader scale, organizations that evaluate proposed studies involving deliberate exposures, whether to pollutants, drugs, medical devices, or treatment methods, usually try to identify the likely beneficiaries. If a test involves a drug, medical device, or treatment method for which an estimated hundreds of thousands of people have been test subjects, the risks of exposure may be offset to some degree by potential benefits to the individual or society.

However, if the primary beneficiary isn't an individual, or even society, but a company that is trying to introduce or expand use of a potentially toxic substance, then the public or individual benefits are extremely low or nonexistent, says Wiles.

A company-funded study came to light in late 2000 when *U.S. News & World Report* covered a Lockheed Martin Corporation study of perchlorate, conducted in response to a class-action lawsuit by residents of Mentone, California, who were concerned about possible health problems from the chemical. Perchlorate, which is found in rocket fuel and some fertilizers, is leaching from a former Lockheed Martin plant near Mentone.

Researchers at the Boston University School of Medicine and Loma Linda Medical Center in California, who were still enrolling volunteers for test exposures in mid-2001, note that perchlorate has been used in thyroid treatments and that the level of test exposure is "many-fold" less than historical thyroid therapy doses. But the test exposure level is still 83 times higher than California standards for site cleanup, said the *U.S. News* article.

Lockheed Martin is helping to clean up Mentone's contaminated groundwater following a mandate from the state. Company officials and researchers declined to release additional information.

The study concerns Wiles, especially if the results are used to allow reduced cleanup standards at the Lockheed Martin site or elsewhere. For example, if testing shows no noticeable effects from doses lower than existing standards, regulatory officials might lean toward lowering standards. People such as Wiles are concerned that limited tests from a focused human study might not account for chronic effects or synergistic actions when people are exposed to other substances in the real world. A similar chain of events has happened with pesticide studies, he notes, with the findings used to relax exposure standards.

However, he does acknowledge that use of human test subjects might be viable if a study evaluated health effects from existing ambient pollutants, such as sulfur dioxide (primarily produced during fossil fuel combustion), and if no other research methods were available.

Sulfur dioxide is one of the substances that Koenig has tested to evaluate its impact on asthma. In a typical study, she recruits 10–40 volunteers, who are exposed one or two times for 5–10 minutes each, she says, with typical exposures in the range of 0.1–1.0 ppm. Many of her volunteers tend to be older people who have time on their hands or who find the study intellectually stimulating. Others have asthma and are curious to know about specific potential irritants. Still others are students who want to make a little money. But the pay is skimpy, $20–30 for most tests, and is designed primarily to compensate subjects for the inconvenience of testing and to pay for their parking. "IRBs don't really like the idea of us 'buying' subjects," she says, particularly if the subjects are children made

available by parents trying to make money.

But some studies pay substantial sums. In the Lockheed Martin study, some subjects are being paid $1,000, according to *U.S. News & World Report*. In another study, conducted in San Francisco to evaluate the effects of ozone on asthmatics, subjects are being offered $1,000 for about 40 hours of time. A recruiting company for the San Francisco study, thehealthexchange.org (one of several hundred such recruiting companies), declined to disclose details of the study, including who is conducting it. But the company's Web site did note that exposures would occur in four-hour stretches and would be at levels equivalent to those in Los Angeles on a smoggy day. The same company also was recruiting in mid-2001 for other studies: one that exposes people to elevated temperatures to test effects on skin circulation, another that exposes people with asthma and chronic obstructive pulmonary disease to air pollutants, and a third that tests the effects of the pesticide permethrin on dust mite allergy and concurrent asthma symptoms.

Pressures from researchers to recruit for studies of all kinds are mounting, according to the HHS Office of Inspector General (OIG), primarily due to increasing demands for more drugs and medical devices, but also due in part to a push by government and individuals for additional knowledge about adverse health effects from the mix of pollutants now present in the environment. The OIG addressed many of the field's problems in a series of reports in 1998, then followed those up with congressional testimony in 2000. OIG officials concluded in 2000 that, along with many other problems with the use of human test subjects, oversight of the recruiting process is limited, and that concerns regarding informed consent, patient confidentiality, and eligibility for enrollment remain.

Making Some Headway

Many researchers and regulatory agencies around the world are focusing on solving the numerous problems that persist with the use of human test subjects. In the United States, members of both the Senate and the House of Representatives are crafting legislative proposals, and more funding will become available for fiscal year 2002. The proposed budget for fiscal year 2002 is expected to be nearly triple the $2.7 million that was available just two years ago, Koski says. The money is all within the budget for the Office for Human Research Protections, and would be used for oversight, education, compliance work, assistance with development of an accreditation program, and other related purposes. Nonetheless, funding remains inadequate, says Heinrich.

However, all these oversight strategies are looking at the problem from the wrong perspective, says Wiles. He believes public health is best protected by more stringent pollutant exposure standards than now exist. Those standards can be tightened based on existing knowledge, he says, and additional testing on humans only helps delay implementation of more protective standards. The idea that human data help tighten pollutant exposure standards is, he says, "sort of naive. Polluters will always find a way to ask for that next study."

If researchers do continue to use human test subjects, government oversight needs to keep improving, Heinrich said in her published testimony: "Overall, HHS's actions appear promising, but we have some concerns about the pace and scope of the department's efforts to ensure the safety and protection of participants in clinical trials." And the onus isn't solely on the government. "There are basic rules," she said while discussing the June 2001 incident at Johns Hopkins. "If investigators aren't following them, the whole system breaks down."

Bob Weinhold

A Laundry List of Concerns

Additional problems that permeate the system for protecting human test subjects, as identified by oversight agencies and independent critics, include:

- lack of a single, independent federal management organization, although sources at the Office for Human Research Protections (OHRP) say that working within the current framework may still be viable if other weaknesses in the system are remedied;
- lack of a unified, comprehensive policy for all types of research involving human test subjects, including studies done by private organizations;
- lack of education among both study participants and researchers about human test subjects, although that is changing, with "an enormous amount of educational activity going on," OHRP sources say, including conference, courses, and intra-agency efforts;
- professional, financial, and ethical conflicts among study sponsors, institutional review boards (IRBs), data monitoring committees, researchers, and test subjects;
- lack of basic information on and accreditation of thousands of institutions and IRBs doing and overseeing research, although a recommendation to have institutions register their IRBs with the Department of Health and Human Services (HHS) is being phased in, and a pilot method for accrediting organizations was recommended in April 2001 by the Institute of Medicine;
- extensive problems in reviewing and reporting adverse events;
- lack of appropriate expertise and suitable points of view on some IRBs;
- lack of funding commitments for IRBs when organizations apply for study approval;
- poor on-site auditing of studies, although the number of visits is up significantly, and is scheduled by the OHRP to continue increasing; even with those increases, however, only a tiny fraction of all research organizations will be audited on-site;
- poor coordination of international studies that may be conducted under varying standards;
- lack of a requirement for complete provision of data by a sponsor before a study begins;
- questionable statistical power in small studies;
- questionable applicability of human tests in understanding chronic health effects (this difficulty may be hard to overcome, as few researchers want to deliberately expose test subjects for any lengthy period);
- infrequent long-term tracking of test subjects to monitor subsequent health effects;
- uneven selection of participants, sometimes targeting those who are otherwise unrepresentative of society and who don't stand to gain proportionately from the research; and
- inadequate penalties for violations, although legislation that would permit civil monetary penalties is under consideration by the HHS; however, the OHRP frowns on fines, favoring oversight and, when necessary, disciplinary action and litigation.